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RN: USAO 2013R00781

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

UNITED STATES OF AMERICA	*	
	*	
v.	*	**CRIMINAL NO.** ELH-19-0282
	*	
ACELL, INC.,	*	**(Failure and Refusal to Report**
	*	**Medical Device Removal, 21 U.S.C.**
Defendant	*	**§§ 331, 333, 360)**
	*	
	*	
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INFORMATION

COUNT ONE
(Failure and Refusal to Report Medical Device Removal)

The United States Attorney for the District of Maryland charges that:

At all times relevant to this Information:

Introduction and General Allegations

1. **ACELL, INC.** (hereinafter, "**ACELL**") was a business corporation organized under the laws of the State of Delaware with its principal place of business in Columbia, Maryland. **ACELL**'s business operations were conducted principally in Columbia, Maryland.

2. **ACELL** engaged in the development, manufacture, processing, packaging, sale, marketing, and interstate distribution of certain medical devices intended for human use throughout the United States, including the District of Maryland.

3. Beginning in or about 2006, **ACELL** engaged in the development, manufacture, processing, packaging, sale, marketing, and interstate distribution of Powder Wound Dressing. **ACELL**'s Powder Wound Dressing was a topical wound dressing derived from ground porcine bladder collagen. **ACELL** marketed Powder Wound Dressing under the trade name

MicroMatrix.

4. Beginning in or about 2011, **ACELL** engaged in the development, manufacture, processing, packaging, sale, marketing, and interstate distribution of PSMX Sheets. **ACELL**'s PSMX Sheets were surgical mesh sheets derived from porcine bladder collagen.

5. The Federal Food, Drug, and Cosmetic Act ("FDCA"), among other things, governed the manufacture and interstate distribution of medical devices for human use.

6. The FDCA required that manufacturers submit certain reports, notifications, and applications to the United States Food and Drug Administration ("FDA") with regard to medical devices. 21 U.S.C. § 360i. Among other things, a manufacturer of a medical device was required to report promptly to FDA any removal of a medical device if the removal was undertaken to reduce a risk to health posed by the device. 21 U.S.C. § 360i(g).

7. Beginning in January 2012 and continuing through at least March 2012, **ACELL** initiated a removal of MicroMatrix to reduce a risk to patient health posed by the device due to endotoxin contamination. **ACELL** management conducted this removal clandestinely, and concealed from doctors and the FDA the endotoxin contamination of MicroMatrix, the removal action, and the attendant risk to patient health. **ACELL**'s "silent recall" placed patients at risk by preventing doctors from making informed medical care decisions concerning the use of **ACELL**'s devices, and preventing the FDA from fulfilling its responsibility of protecting public health and safety.

FDA Regulatory Background

8. The FDA was the federal agency responsible for protecting the health and safety of the American public by enforcing the FDCA and assuring, among other things, that medical devices intended for use in the treatment of human beings were safe and effective for their intended uses. Pursuant to its statutory mandate, the FDA regulated the manufacture,

processing, packing, labeling, and shipment in interstate commerce of medical devices.

9. The FDCA and its implementing regulations prohibited manufacturers from distributing in interstate commerce any medical device unless the FDA had granted marketing authorization for the device or the device was covered by an exemption not applicable here. There generally were two ways for a manufacturer to obtain FDA marketing authorization for a medical device.

10. The first way for a manufacturer to obtain authorization to distribute a medical device was by receiving FDA approval of the manufacturer's application for pre-market approval of the device ("PMA approval"). The FDA would not grant PMA approval unless the information in the PMA application provided the FDA with reasonable assurance that the device was safe and effective for its intended use, as reflected in its FDA-approved labeling.

11. The second way for a manufacturer to obtain authorization to distribute a medical device was by receiving FDA clearance that the medical device was substantially equivalent to a device that already was legally being marketed, *i.e.*, a "predicate device." This process was referred to as "510(k) clearance." The FDA would grant 510(k) clearance if it determined, among other things, that the device had the same intended use as the predicate device and did not raise new issues of safety or effectiveness.

12. The PMA approval process often required that manufacturers submit the results of clinical testing on human subjects to the FDA. The 510(k) clearance process did not usually require the submission of such data.

13. Regardless of the route chosen by a device manufacturer in seeking the FDA's approval to market a medical device, a device manufacturer's application to the FDA was required to contain proposed labeling sufficient to describe the device, its proposed indication for use, and the directions for its proposed indication for use. Any FDA clearance or approval of a

device was based on and limited to a specific and defined indication for use. Later, if a device manufacturer wanted to market a device for an expanded or different indication than that approved or cleared by the FDA, the device manufacturer would be required to seek further marketing authorization from the FDA through an additional approval or clearance application.

14. After receiving approval or clearance to market a medical device, a device manufacturer was required to establish and maintain records, make reports, and provide information to the FDA in order to assure the continued safety and effectiveness of its device. In addition, a device manufacturer was required promptly to report to the FDA certain removals of a medical device from the market.

15. Specifically, the FDCA and its implementing regulations required that **ACELL**, as a medical device manufacturer, submit a written report to the FDA within ten days of initiating any removal of a device undertaken to reduce a risk to health posed by the device. 21 U.S.C. § 360i(g); 21 C.F.R. § 806.10. The failure or refusal to make such a report was a prohibited act under the FDCA. 21 U.S.C. § 331(q)(1).

16. "*Removal* means the physical removal of a device from its point of use to some other location for repair, modification, adjustment, relabeling, destruction, or inspection." 21 C.F.R. § 806.2(j) (italics in original).

17. "*Risk to health* means (1) a reasonable probability that use of, or exposure to the product will cause serious adverse health consequences or death; or (2) that use of, or exposure to, the product may cause temporary or medically reversible adverse health consequences, or an outcome where the probability of serious health consequences is remote." 21 C.F.R. § 806.2(k) (italics in original).

ACELL's Devices

18. **ACELL** manufactured multiple medical devices that were derived from porcine

urinary bladder material, including devices that were cleared for internal surgical implantation and devices that were cleared only as topical wound dressings.

19. **ACELL**'s PSMX Sheets were sterilized, dried sheets of porcine bladder material. The PSMX Sheets were produced by layering multiple sheets of porcine bladder material atop each other to produce a single, thicker, sheet. The PSMX Sheets were cleared for "implantation to reinforce tissue where weakness existed in urological, gynecological, and gastrointestinal anatomy, including, but not limited to the following procedures: pubourethral support, tissue repair, body wall repair, and esophageal repair."

20. **ACELL**'s MicroMatrix was produced by grinding bladder sheets into a particulate, and was cleared only for "the management of topical wounds." MicroMatrix was packaged into vials and sold in quantities ranging from 20 mg to 1,000 mg.

21. Both PSMX Sheets and MicroMatrix are devices as defined in the FDCA. *See* 21 U.S.C. § 321(h).

The FDA Clearance Process for ACELL's MicroMatrix

22. On or about March 31, 2006, **ACELL** submitted a 510(k) premarket notification to the FDA requesting clearance to market MicroMatrix.

23. After evaluating **ACELL**'s initial 510(k) submission for MicroMatrix, the FDA expressed concern about **ACELL**'s proposed indication for the device. In a May 19, 2006 letter to **ACELL**, the FDA informed the company that, "[t]he predicate device, K030921, states in the device name 'topical wound dressing.' The subject device does not have any statement regarding topical use. Please include as part of the device name or in the indication for use a [phrase] that states 'for skin surface wounds.' You need to be clear that this device is not intended for internal use; otherwise, this indication would require a premarket application."

24. In response to the FDA's request, **ACELL** modified MicroMatrix's proposed

indication for use statement to include the word "topical," clarifying that MicroMatrix was intended for topical use only and not intended for internal use.

25. Upon receipt of **ACELL**'s clarification that the device was intended only for topical use, on or about June 23, 2006, the FDA cleared MicroMatrix via 510k number K060888. The FDA clearance letter accompanying 510k number K060888 explicitly stated that MicroMatrix was indicated only for "the management of topical wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears), and draining wounds."

ACELL's Development of a Market for Non-FDA Cleared Uses of MicroMatrix

26. Despite the FDA's warning that **ACELL** would need to submit an application for PMA if it intended to market its MicroMatrix for internal uses, **ACELL** management directed and incentivized its sales force to sell MicroMatrix for a variety of internal uses that the FDA had not cleared.

27. **ACELL** senior management knew that physicians used MicroMatrix on patients internally, including injecting MicroMatrix into the bodies of patients in applications such as hair restoration and orthopedic procedures, and implanting MicroMatrix into patients in conjunction with PSMX Sheets.

28. **ACELL** used various means to educate its sales force about strategies to market and sell MicroMatrix for internal uses, including through the specific means of weekly teleconference programs called "Bladder Matters." During Bladder Matters calls, featured sales representatives provided advice to **ACELL**'s sales force on how best to maximize product sales, and gave case history presentations demonstrating particularly notable uses of **ACELL** product.

As an accompaniment to the case history presentations, **ACELL** management distributed PowerPoint presentations depicting how **ACELL** product was utilized in each procedure. **ACELL** management selected the sales representatives to give case history presentations, and reviewed and vetted the accompanying PowerPoint presentations distributed to the sales force. These case history presentations at times featured internal usage of MicroMatrix.

29. Bladder Matters calls and PowerPoint presentations featured discussions and depictions of the use of MicroMatrix in combination with PSMX Sheets that the FDA had not cleared. PSMX sheets were indicated for surgical procedures, and doctors used PSMX sheets in internal surgical procedures. MicroMatrix was indicated for topical use only. Nevertheless, the Bladder Matters calls and PowerPoint presentations described surgical procedures in which MicroMatrix was implanted deeper into the human body than the PSMX sheets, and the PSMX sheets were then overlaid atop MicroMatrix. **ACELL** encouraged its sales force to promote MicroMatrix for this combination use with PSMX Sheets.

30. **ACELL** also encouraged the use of MicroMatrix in internal procedures by targeting and hiring certain sales representatives who possessed preexisting relationships with physicians specializing in areas of medicine for which **ACELL** had no FDA-cleared product, including but not limited to dermatological and orthopedic injections.

31. None of these internal uses were included in the scope of the MicroMatrix 510(k) clearance. In fact, during the clearance process, the FDA had explicitly warned **ACELL** that if it intended to distribute MicroMatrix for such internal uses, **ACELL** was required to submit a PMA application to the FDA.

Endotoxin Contamination of ACELL's Products

32. Endotoxins are complex pyrogenic toxins located in the cell walls of gram-negative bacteria. Endotoxins are released from bacterial cell walls as a byproduct of sterilization

processes.

33. The effects of endotoxin exposure on the human body are significant and dangerous, and include fever, infection, septic shock, and death.

34. In recognition of the risk to health posed by endotoxins, FDA guidance and industry standards set limits capping the acceptable level of endotoxins in a given medical device. These endotoxin limits were based upon the device's intended use. For most medical devices, including devices that were intended for surgical implantation into the body, FDA guidance and industry standards allowed no more than 20 endotoxin units ("EU") per device. In contrast, FDA guidance and industry standards did not limit the amount of endotoxins that were allowable on medical devices that were intended to be used only as topical wound dressings. The potential harm posed by endotoxin exposure on the external skin surface was comparatively low when compared with the risk to health from internal exposure.

35. In or about March 2011, **ACELL** performed testing on certain lots of MicroMatrix and discovered endotoxin levels in excess of 20 EU per device. Testing revealed endotoxin levels up to 90 EU per device in the sampled lots. Subsequent testing in May 2011 revealed endotoxin levels up to 272 EU per device in additional sampled lots.

36. In or about June 2011, **ACELL** discovered levels of endotoxin on PSMX Sheets in excess of 20 EU per device. **ACELL** calculated that the largest size PSMX Sheets could have endotoxin levels up to 128 EU per device, more than six times the limit set by FDA guidance and industry standards. **ACELL** removed the PSMX Sheets from the market after concluding that the elevated levels of endotoxin on the PSMX Sheets posed a significant and serious risk to patient health. **ACELL** also assigned a team of scientists from the Research and Development department ("**ACELL** scientists") to investigate the source of the endotoxin contamination and implement solutions.

37. On July 6, 2011, **ACELL** notified the FDA that it was recalling the PSMX Sheets due to the health risk posed by elevated levels of endotoxin on the devices. Specifically, in its Recall Notification to the FDA, **ACELL** stated that "[e]ndotoxins . . . are substances . . . that, at elevated levels, can cause serious illness which can be fatal" and "[e]levated endotoxin levels may cause fever, serious adverse health consequences or death."

38. In response to **ACELL**'s Recall Notification, the FDA conducted a Health Hazard Evaluation on the recalled PSMX Sheets and found that, "[t]he immediate and long term health consequences of these defects/malfunctions include fever, patient infection, implant failure requiring surgical intervention, other patient reactions including inflammation, and death."

39. As part of its efforts to recall the PSMX Sheets, **ACELL** removed approximately 292 devices from its internal warehouse inventory and warned approximately 24 doctors, who had previously received affected devices, that the PSMX Sheets they had implanted into patients were potentially contaminated by elevated levels of endotoxin. **ACELL** also published a statement on its website notifying the public about the problem.

40. **ACELL** took no action, however, to recall or remove the MicroMatrix discovered in March 2011 to have elevated levels of endotoxin.

ACELL's Removal of Contaminated MicroMatrix from the Market

41. In or about January 2012, **ACELL** submitted multiple MicroMatrix devices to a third-party testing company to determine the amount of endotoxin present on the powder. The test results affirmed that the endotoxin contamination of MicroMatrix affected a wider range of production lots than those implicated in the June 2011 endotoxin testing of PSMX sheets. The test results revealed endotoxin levels above the 20 EU limit for internal use in MicroMatrix packaged in 100 mg, 200 mg, 500 mg, and 1,000 mg volumes that spanned a wide range of

production lots and affected over 30,000 devices. The new test results also demonstrated endotoxin levels up to 626 EU per device, over thirty times in excess of the FDA guidance and industry standard limits of 20 EU per device, for devices used internally.

42. On or about January 16, 2012, **ACELL** scientists concluded that the contaminated MicroMatrix posed a health risk. In a series of meetings, **ACELL** scientific and quality employees presented their findings to **ACELL** senior management and suggested that MicroMatrix be recalled from the market.

43. **ACELL** senior management reviewed the findings and recommendations of the investigatory team and concluded that the high levels of endotoxin present in MicroMatrix posed a risk to patient health.

44. **ACELL** senior management knew that even devices as small as 100 mg and 200 mg from the affected lots of MicroMatrix were contaminated by endotoxin levels above the 20 EU limit and posed a risk to patient health. Yet **ACELL** senior management removed only 500 mg and 1,000 mg MicroMatrix devices sourced from the lots contaminated by high levels of endotoxin from the market because **ACELL** senior management knew that 500 mg and 1000 mg MicroMatrix devices were used internally.

45. On January 27, 2012, **ACELL** initiated the removal of the contaminated lots by instructing its sales representatives to return all 500 mg and 1,000 mg volumes of MicroMatrix to **ACELL**'s corporate headquarters. **ACELL** instructed its sales force to return product that was held in the sales representatives' personal inventories and product that was held on consignment at the point of use at hospitals and other healthcare facilities.

46. **ACELL** did not instruct its sales representatives to return any volumes of MicroMatrix smaller than 500 mg. Instead, **ACELL** left the smaller volumes on the market and made no effort to inform doctors that the smaller volumes of MicroMatrix were contaminated by

endotoxin.

47. Over the following several weeks, **ACELL** sales representatives returned their inventories of 500 mg and 1,000 mg vials of MicroMatrix to **ACELL**'s corporate headquarters. Among other things, these sales representatives removed MicroMatrix sourced from the contaminated lots from its point of use at hospitals and doctors' offices and shipped it back to **ACELL** corporate headquarters in Maryland.

48. When MicroMatrix sourced from the contaminated lots was returned to and received at **ACELL**'s corporate headquarters in Maryland, **ACELL** employees placed it in a designated "quarantine area." Subsequently, at the direction of **ACELL** senior management, including **ACELL**'s President, **ACELL** employees removed certain vials of MicroMatrix from the quarantine area and redistributed them to veterinarians. **ACELL** neither informed these veterinarians that the MicroMatrix was from lots with elevated endotoxin levels nor that the MicroMatrix had been removed from the human medicine market.

49. Some portion of the contaminated MicroMatrix that had been placed into the quarantine area and not redistributed to veterinarians was destroyed.

ACELL Senior Management Did Not Disclose the Elevated Levels of Endotoxin in MicroMatrix

50. **ACELL** senior management concealed from **ACELL**'s sales force that certain lots of MicroMatrix were contaminated with endotoxin and posed a risk to patient health. Rather, **ACELL** sent sales representatives personalized e-mails that stated, "**ACELL** Corporate is establishing minimum and maximum inventory levels for all **ACELL** field reps, during this time we will be asking you to recycle your current inventory starting with MicroMatrix devices." Each e-mail then listed the quantities of 500 mg and 1,000 mg vials of MicroMatrix that the sales representative had in his or her product inventory, and instructed the representative to

return the entire quantity to **ACELL**'s corporate headquarters.

51. **ACELL** sales representatives did not know that the MicroMatrix they were instructed to return to company headquarters had elevated endotoxin levels. As a result, some sales representatives delayed returning their inventory and continued to distribute MicroMatrix from contaminated lots after being told to return their inventory. **ACELL** senior management did not inform these sales representatives that the MicroMatrix they had sold and were continuing to sell to doctors was from contaminated lots.

52. **ACELL** also concealed the product contamination and removal from doctors and hospitals. Specifically, **ACELL** did not disclose to doctors and hospitals the fact that the removal of MicroMatrix consignment stock was due to endotoxin contamination. Among other things, **ACELL**'s management, at the direction of **ACELL**'s President, instructed at least one sales representative to "tell the hospital he is just updating product, that we cycle inventory to prevent any product from sitting on the shelves too long."

53. **ACELL** senior management did not disclose to doctors who continued to buy and use or had used 500 mg and 1,000 mg vials of MicroMatrix that **ACELL** sold and continued to sell product that was subject to a removal action.

54. **ACELL** sales representatives continued to distribute 100 mg and 200 mg vials of MicroMatrix that were derived from the contaminated range of production lots. **ACELL** management concealed from doctors receiving these devices that the lots were contaminated, and that **ACELL** had conducted a removal of devices of larger vial sizes due to the risk to patient health posed by endotoxin-contaminated devices used internally. **ACELL** senior management directed the continued distribution of the 100 mg and 200 mg vials despite warnings from **ACELL** scientific and quality employees that these volumes posed the same risk to patient health. Upon being told of the risk to patient health posed by the 100 mg and 200 mg

vials of MicroMatrix, **ACELL**'s CEO stated that the devices had "too much street value" to be removed from the market.

55. **ACELL** also concealed important safety information from medical professionals who reported adverse events. **ACELL** received product-related complaints from several medical professionals, including doctors, a veterinarian, and a nurse, who had used MicroMatrix sourced from contaminated lots on patients. These medical professionals reported to **ACELL** adverse events in which patients displayed symptoms consistent with endotoxin exposure, such as fever and inflammation. Various **ACELL** employees, including in some instances **ACELL**'s President, personally discussed the adverse events with these medical professionals, yet did not inform them that the MicroMatrix they had used was sourced from contaminated lots and the adverse events could potentially be caused by the contaminated MicroMatrix. **ACELL** did not memorialize in company complaint files the fact that the MicroMatrix at issue in these adverse events was sourced from contaminated lots.

56. Collectively, **ACELL** did not disclose to doctors, veterinarians, nurses, and hospitals important safety information concerning MicroMatrix that was being used on patients during surgical procedures. By concealing this information, **ACELL** prevented these medical professionals and hospitals from making informed decisions regarding their purchase and use of **ACELL**'s products.

57. **ACELL** did not submit a notification to the FDA informing the agency that it had removed 500 mg and 1000 mg volumes of MicroMatrix. In contrast, in connection with the prior July 8, 2011 recall of PSMX Sheets, **ACELL** did submit a removal notification to the FDA. Thus, **ACELL** was aware of its obligation to inform the FDA of removals undertaken to reduce a risk to public health.

58. By performing a silent recall of MicroMatrix and not informing the FDA,

ACELL prevented the FDA from fulfilling its public health responsibility to evaluate whether the actions taken by the company and its management were adequate to protect patient health and safety and interfered with the FDA's ability to take further actions against **ACELL**'s products.

59. **ACELL** senior management knew that if it had recalled the endotoxin contaminated MicroMatrix in the same manner as the PSMX Sheets, **ACELL** would have had to remove every device contaminated by endotoxins, including the 100 mg and 200 mg volumes. **ACELL** also would have had to directly notify every doctor who had purchased the contaminated MicroMatrix. In contrast with the PSMX Sheet recall, in which **ACELL** notified approximately 24 doctors, **ACELL** would have had to notify many more doctors who had purchased the contaminated MicroMatrix.

60. Under the FDCA and its regulations, **ACELL**'s silent recall of MicroMatrix on or about January 27, 2012, was a removal undertaken to reduce a risk to health posed by the device.

61. **ACELL** was required to report this removal to the FDA in writing within ten working days of initiating it. 21 U.S.C. § 360i(g); 21 C.F.R. § 806.10. The report of removal was required to include, inter alia, "[a] description of the event(s) giving rise to the information reported" and "[a]ny illness or injuries that have occurred with use of the device." 21 C.F.R. § 806.10.

62. **ACELL** failed and refused to furnish this required report to the FDA.

The Charge

63. On or about January 27, 2012, in the District of Maryland and elsewhere, the defendant,

ACELL, INC.,

did fail and refuse to furnish a notification and other material and information required by and under Title 21, United States Code, Section 360i, in that the defendant failed to submit a written report to FDA of a removal of **ACELL**'s Powder Wound Dressing, which removal was undertaken by the defendant to reduce a risk to health posed by the device.

21 U.S.C. § 331(q)(1)(B)
21 U.S.C. § 360i(g)
21 U.S.C. § 333(a)(1)

6/6/19
Date

Robert K. Hur
Robert K. Hur
United States Attorney

6/5/19
Date

Gustav W. Eyler
Gustav W. Eyler
Director, Consumer Protection Branch
U.S. Department of Justice